

Current Status of *H. pylori* Infection Treatment 2017

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ABSTRACT

H. pylori infection is highly associated with main symptoms and death that are recently affecting 50-75% of the population in the world. But past few years' efforts, *H. pylori* treatment is more difficult and it is still standing challenges for medical practitioner due to antibiotic resistance and patient compliance, as there are no regimens can achieve the desired eradication rate. In fact, no new drug has been developed for *H. pylori* only using different mixtures of antibiotics and anti-secretory agents. Nowadays, antibiotics are frequently prescribed for this infection that is declining their effectiveness as a result of which growing antibiotic resistant worldwide. At present, standard therapy has been regarded as the first line treatment of *H. pylori* in many guidelines, but the eradication rate has decreased to unacceptable levels. Therefore, standard triple therapy is left due to increase in antibiotic resistance consequences low eradication rate. Alternative treatment regimens such as sequential, quadruple, concomitant, and levofloxacin therapies are most recommended eradicating *H. pylori* compare to triple therapy; one of them levofloxacin therapy is most excellent therapy for eradicating *H. pylori* infection in antibiotic resistant patients. Herein, this review discussed recent data focusing on diverse eradication regimens so as to emphasize the current *H. pylori* treatment and the significance of considering the occurrence of antibiotic resistance at a regional level when choosing a suitable therapy.

INTRODUCTION

H. pylori infection is a pathogenic bacterium which lives in the acidic condition of the gastrointestinal. Some researchers suggested that it is recognized as the most common chronic human bacterial infection (Zhao *et al.*, 2014; Tan *et al.*, 2011). It was the first exposed and acknowledged in 1982 by the Australian scientists Barry Marshall and Robin Warren (Nicholas Martinez *et al.*, 2014).

One of the leading causes of infection around the world is due to the bacteria infection. *H. pylori* infection is nearly 50-75% affected of the worldwide demography, in the developing countries 70% of people are affected, whereas the percentages little lower, (25-50%) in the developed countries (Safavi *et al.*, 2016; Zhao *et al.*, 2014). It is mainly attained earlier (about previously 10 years) and persist life. Most children are minor

extent affecting *H. pylori* from their mother, siblings, and fathers and also transmitted into the gastrointestinal tract to the oral cavity (e.g., Expression to vomit) and fecal to oral pathway from human beings to human beings. However, the incidence of this infection is not homogeneous international (Neil *et al.*, 2014; Pacifico *et al.*, 2010). The prevalence of *H. Pylori* infection is associated with lower social, financial situation, sanitation, basic hygiene, a poor diet, overcrowding, ethnicity, gender and age, low levels of education and geographic location which a major role in the distribution of infection (Sally *et al.*, 2013; David *et al.*, 2014).

The global occurrence of HP infection is related to more affect South America (30-90%) such as Chile and Brazil than North America (30-90%) as well as in Europe 1.2-70% (for example, in the Netherlands 1.2%) is less than in the Middle East 50-94% (in most cases in Albania, Bulgaria, and Estonia). In contrast, the prevalence rate is lower in Australia (15-20%) than in Africa (48-95%) usually in Ethiopia and it is more prevalent in China up to 60 years old (86%), as well as those vegetarian persons are amazingly more prevalent.

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The annual report that *H. pylori* re-infection rate is greater in Asia (4.3-13%) than the west (0.5-2.5) (Ramesh *et al.*, 2017). In Asia, studies shown that the prevalence of *H. pylori* infection rates are slightly higher more population country (58% in China, 60% in South Korea, 75% in Vietnam, 79% in India, and 92% in Bangladesh) than lower population (31% in Singapore, 36% in Malaysia, 39% in Japan, 55% in Taiwan, 57% in Thailand)(Yang *et al.*, 2014).

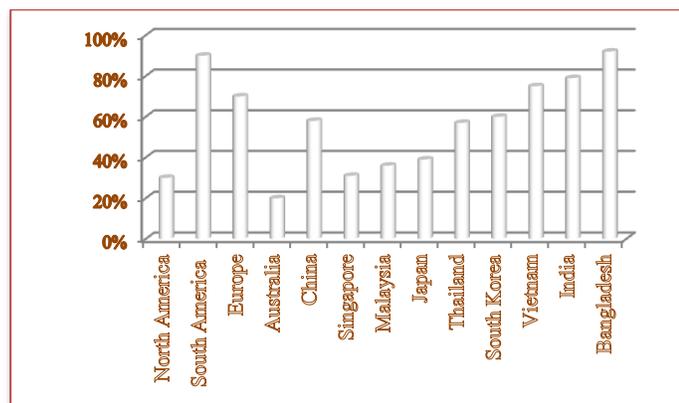


Fig. 1: Worldwide incidence rates for *H. pylori* infection.

H. pylori infection can lead to a different upper gastrointestinal disorder such as gastric inflammation (gastritis), heartburn, gastroesophageal reflux disease, gastric duodenal ulcer disease, gastric cancer and mucosa-associated lymphoid tissue (MALT). Up to 76-95% of gastric cancers and 90% of duodenal ulcer is associated with *H. pylori* infection (Zhao *et al.*, 2014; Ramesh *et al.*, 2017; Sollano *et al.*, 2015). Most infection, patients are asymptomatic and 10-15% patients infected on the increase chronic inflammation lead to atrophic gastritis, peptic ulcer in addition to gastric adenocarcinoma (Partha *et al.*, 2016). There are different approaches for the eradication of infection caused by *H. pylori*. One of the widely used methods is several combined antibiotics, such as amoxicillin plus clarithromycin or metronidazole with a proton-pump inhibitor (Safavi *et al.*, 2016). At present, the eradication of *H. pylori* infection is main troubles antibiotic resistance, patients compliance and intolerance to therapeutic regimens (Niv *et al.*, 2015). Antibiotic resistance is nowadays a major concern since one of the major causes of treatment failure against the *H. pylori* is drugs sensitive to this germ are getting resistant (De Francesco *et al.*, 2010; Caliskan *et al.*, 2015; Filipa *et al.*, 2011). The causes of resistance are poor drug penetration, low drug concentration, short gastric residence time and antibiotic resistance represent a significant health care burden on society. Besides, the poor stability of antibiotics in gastric content requires frequent administration and leads to patient noncompliance (David *et al.*, 2014). An ideal treatment of *H. pylori* infection has still to be found. At present, it is necessitated to develop making a new drug that is improving therapeutic efficacy (Hajiani *et al.*, 2009; Michael *et al.*, 2008).

The successful and complete eradication of *H. pylori* infection has become a challenging malignant disease worldwide

(Lu *et al.*, 2014). There are different types of therapies using treatment of *H. pylori* infection such as standard, sequential, quadruple, concomitant and levofloxacin therapy. Those therapies are even the best for the treatment of this infection that is assure patient compliance to increase the high cure rate. But standard triple therapy has been recently declined efficacy due to antibiotic resistance resulting decreased eradication rates. Bismuth quadruple, concomitant, sequential and levofloxacin therapies are currently better than standard therapy that is providing promoted efficacy (Ermis *et al.*, 2015; Papastergiou *et al.*, 2014; Benjamin *et al.*, 2010). Therefore, this study major purposed to provide a reconsideration modern beneficial efficacy of the drug and better eradication rates of *H. pylori* infection.

The recommended doses of standard, sequential, Quadruple bismuth, Concomitant and levofloxacin therapy drugs for treatment of *H. pylori* infection is shown in Table 1.

Table 1: Current regimen for treatment of *H. pylori* infection.

Standard regimen (7-14 d)	
1.	A PPI (standard dose, bid)+ amoxicillin (1 g, bid) + clarithromycin (500 mg, bid).
2.	A PPI (standard dose, bid) + metronidazole (400mg, bid) + clarithromycin (500 mg, bid).
3.	A PPI (standard dose, bid) + amoxicillin (1 g, bid) + metronidazole (400 mg, bid).
4.	PPI (standard dose, bid) + amoxicillin (1 g, bid) + furazolidone (200 mg, bid).
Sequential regimen (5 d)	
1	APPI (standard dose, bid) + amoxicillin (1 g, bid).
2	A PPI (standard dose, bid) + amoxicillin (1 g, bid) followed by PPI + clarithromycin (500 mg) + metronidazole(500 mg).
3	PPI (standard dose, bid) + amoxicillin (1 g, bid) followed by PPI + clarithromycin (500 mg) + tinidazole (500 mg).
Quadruple bismuth regimen (7, 10-14 d)	
1	A PPI (standard dose, bid) + bismuth (240 mg, bid) + amoxicillin (1 g, bid) + furazolidone (20 mg, bid).
2	A PPI (standard dose, bid) + bismuth (240 mg, bid) + amoxicillin (1 g, bid) + metronidazole (400 mg, bid).
3	A PPI (standard dose, bid) + bismuth (240 mg, qid) + Tetracycline (500 mg, qid) + Metronidazole (500 mg, tid).
4	A PPI (standard dose, bid) + bismuth subsalicylate (525 mg, qid) + metronidazole (250 mg, qid) + tetracycline (500 mg, qid).
5	Rabeprazole (40 mg, bid) + bismuth potassium citrate (220 mg, bid) + metronidazole (500 mg, tid) + tetracycline (500 mg, tid).
Concomitant regimen (7-10 d)	
1	A PPI (standard dose, bid) + Clarithromycin (500 mg, bid) + Amoxicillin (1 g, bid) + Metronidazole (500 mg, bid) + tinidazole (500 mg, bid).
	Sitafloxacin therapy (7-d)
2	A PPI (standard dose, bid) + amoxicillin (750 mg, bid) + sitafloxacin (100 mg, bid).
Levofloxacin regimen (5-7 d)	
1	A PPI (standard dose, bid) + levofloxacin (500 mg, bid)+ either amoxicillin (1000 mg or tinidazole 500 mg, bid).
2	Esomeprazole (40 mg, bid) + amoxicillin (1 g, bid) followed by esomeprazole (40 mg, bid) + levofloxacin (240 mg, bid) + metronidazole (500 mg, bid).
3	Esomeprazole (20 mg, bid) + amoxicillin (1 g, bid) + levofloxacin (250 mg, bid)
4	Esomeprazole (40 mg, bid) + amoxicillin (1000 mg, bid)+levofloxacin (500 mg, bid)

Abbreviation: PPI: Proton pump inhibitor, *bid*: Twice daily, *qid*: Four times daily, *tid*: Three times daily, *d*: days.

First-line therapy

Selection of drug for *H. pylori* infection regimens are influenced by diverse reasons involving efficacy, patient tolerance, existing antibiotic resistance, and worth of the drugs. Eradication rate should lead to 90% against *H. pylori* infection (Malekzadeh *et al.*, 2004). Standard regimen such as clarithromycin plus proton pump inhibitor (PPI) plus amoxicillin or metronidazole for 7, 10 and 14 days is worldwide followed by first-line treatment regimen. It has revealed that PPI-based triple regimen which provided eradication rates greater than 80-90%, usually consisting of a PPI, amoxicillin, and clarithromycin (Papastergiou *et al.*, 2014). The recent national survey reported that the eradication rate of triple therapy, which is 84.92–87.50% from 2001 to 2007, but 80–81.43% from 2008 to 2010 (Sherief *et al.*, 2016). Review studies have shown that eradication rate is highest using amoxicillin with PPI and clarithromycin (83.50%) than metronidazole 68.64% as well as PPI, amoxicillin, and metronidazole the rate 82%; each therapy lasting 14 days (Ermiş *et al.*, 2015).

The combination of antibiotics with PPI is still the best regimen in Hong Kong for 7 days administration and their eradication rate is 92.7% (Benjamin *et al.*, 2010). Several studies have shown that in Europe, Canada is better efficacy (greater than 80%) than Iranian (lower than 60%), eradication rate is 76% for PPI, amoxicillin, and furazolidone in Iranian (Malekzadeh *et al.*, 2004). In contrast, it found that the eradication rate is insufficiently less (lower than 45-60%) in a few countries (Vaira *et al.*, 2009). In Italian studies reported that triple therapies gain disappointing eradication rate, with a value lower than 80% and the standard 14-days triple therapy cure rate is 70-81.70%, whereas it seen that eradication rate is 74.80-82.22% obtained in different countries, such as Germany, Korea, and Latin America (De Francesco *et al.*, 2016).

At present, reduction of the eradication rate with standard triple therapy due to antibiotic resistance which is reporting that lower than 80% (Yoon *et al.*, 2016). The Amoxicillin resistance rate is 6.30-14.93% and clarithromycin rate is 23.70-71.20% during the period of 2003-2012. In recently proposed that the clarithromycin resistance rates in American, European, Turkey and South America populations are 29.3%, 11.1%, 47.5% and 17.2% and metronidazole resistance rates in Chinese population are 75.6-95.4% whereas in Japan is 3.3-12.9%. Recently viewed that amoxicillin resistance rate is comparatively declining almost 1-5% in China and in more developed countries. Several studies have shown that antibiotic resistance and poor compliance due to treatment failure of this infection. As a result, first line therapy decrease eradication rates worldwide against *H. pylori* during the last few years (Kim *et al.*, 2015, Chang *et al.*, 2017, Zhang *et al.*, 2015). Their cure rate is declining (50-60%) for PPI, amoxicillin, and clarithromycin due to resistance to clarithromycin and metronidazole and their rate 38.5% in a turkey study (Dolapcioglu *et al.*, 2014). In Japan, 7 days triple therapy cure rate is 60–70% due to widespread clarithromycin resistant (Hirata *et al.*, 2016). Consequently, various ways have been recommended in order to avoid treatment failure of triple therapy, included in the treatment

of duration, PPI effect on gastric acid secretion, other drug resistance and the patient's compliance. Esomeprazole is more anti-secretory effects of *H. pylori* eradication than other PPIs such as omeprazole, lansoprazole, and pantoprazole (Niv *et al.*, 2015). Another currently approach to use sequential and quadruple bismuth therapy have better eradication rates for the *H. pylori* treatments compared to triple therapy (Doffou *et al.*, 2015).

Sequential therapy

Sequential therapy is more effective in eradicating *H. pylori* infection instead of standard triple therapy and it is gaining a high eradication rate for administration either 7 or 10 day triple therapy. Sequential therapy actually second line treatment, for example, a proton pump inhibitor (PPI) plus amoxicillin 1 g according to a triple therapy, including a PPI with clarithromycin and tinidazole is given for 5 days and their eradication rates are 91% and 93%. On the contrary, changing the drug metronidazole used to give poor consequence compared to tinidazole and their eradication rate is 84% and 97%. It has reported that the eradication rate of sequential therapy is more than 90% (Yoon *et al.*, 2016; Vaira *et al.*, 2009). In a recent, studies showed that eradication rate is higher for 5 days than 7- 10 days (De Francesco *et al.*, 2014). Nowadays, it is developed to overcome standard therapy, antibiotic resistance against *H. pylori* their eradication rate is 63% and 71% for standard and sequential therapy (Dolapcioglu *et al.*, 2014). Sequential therapy is fruitful in children and elderly patients (Lee *et al.*, 2016).

But some studies reported that sequential and standard triple therapies are corresponding patient compliance and side effects. Patient compliance is little lower in sequential therapy (92.6%) than standard therapy (94%). On the other hand, side effects are more in sequential therapy (9.9) than standard therapy (9.8%). Amoxicillin is more effective than other drugs due to low resistance rate and high pH environment. Some studies demonstrated that high-dose a PPI plus amoxicillin is overcoming resistance rate and their eradication rate is 72 -81% (Safavi *et al.*, 2016; Vaira *et al.*, 2009). Recently, studies found that it is highly eradicating of *H. pylori* infection compared to first line therapy; after it cannot achieve in therapeutic efficacy treatment of this infection due to antibiotic bacterial resistance smoking and nonclear dyspepsia (Zullo *et al.*, 2006).

Quadruple bismuth therapy

Bismuth-based quadruple therapy has been most excellent as regards the eradication rate because it is easily released into the gastric mucous layer with a low antibiotics resistance rate (Sarkeshikian *et al.*, 2013; Jo *et al.*, 2008). A quadruple therapy is consisting of bismuth, a PPI, and two antibiotics and their cure rate is 85-92% from Iranian to Netherlands (Malekzadeh *et al.*, 2004). For example, combined with a PPI, bismuth subsalicylate, metronidazole and tetracycline for 10-14 days and their eradication rate is more than 95% (Ermiş *et al.*, 2015). Other studies showed that eradication rate is 87-90% for PPI, bismuth, metronidazole, tetracycline (Nicholas *et al.*,

2014; Wong *et al.*, 2016). In Turkey, studies reported that eradication rate is 94.2% for rabeprazole plus bismuth potassium citrate plus metronidazole plus and tetracycline given for 10 days, which recommended in the addition of bismuth can overcome difficult to clarithromycin resistant (Ayse *et al.*, 2016).

Bismuth-based treatment may become sufficient until given with a PPI and cannot be recommended even because of long-term efficacy has not been found, but when furazolidone with bismuth is planned to combine for use in quadruple therapies resulting considerable side effects (Hajiani *et al.*, 2009). Nevertheless, quadruple therapy is recently fall off treatment of *H. pylori* infection in nearly 20 to 30% patients due to two antibiotic resistance such as clarithromycin and metronidazole resistance (Gisbert *et al.*, 2012). Recently found that quadruple therapy with PPI plus a single capsule containing three antibiotics (bismuth subcitrate, metronidazole, and tetracycline) is acquired a better eradication rate (92-93%) and overwhelming metronidazole resistance (Manfredi *et al.*, 2013).

Concomitant therapy

Concomitant therapy is an alternative treatment for standard triple therapy and it is the higher eradication rate (90%) than standard triple therapy. In these therapies are providing three antibiotics with a PPI for 10 days such as esomeprazole plus amoxicillin plus clarithromycin and metronidazole have significantly superior eradication rates of 89% and 93%. In a recent provide that dual drug resistance is 100% clarithromycin, 91% metronidazole and 25% clarithromycin, metronidazole 40%, eradication rate are only 55% and 90% with concomitant therapy (Ramesh *et al.*, 2017; Ermis *et al.*, 2015). Different studies demonstrated that Concomitant therapy is the higher eradication administration for 5 days (De Francesco *et al.*, 2014). Some studies have shown that the concomitant and sequential therapies are about same therapeutic effects and patient compliance, but patient compliance is little more than sequential (Lee *et al.*, 2016). Several studies demonstrated that concomitant and sequential therapies are nearly uniform eradication rates and their eradication rates are 92.3% and 93% (Nicholas *et al.*, 2014). On the other hand, concomitant therapy is more active and higher eradication rate

about (90%) than sequential therapy for antibiotic resistance patients, even high clarithromycin and metronidazole resistance (Julia *et al.*, 2015).

Levofloxacin therapy

Levofloxacin is a broad-spectrum fluoroquinolone antimicrobial agent which inhibits the DNA synthesis and well tolerated (Cianci *et al.*, 2006; Gisbert *et al.*, 2006). Levofloxacin therapy is superior efficacy than triple therapy study in the US and it is the best treatment for *H. pylori* antibiotic resistance infected patients, especially metronidazole resistance (76%) and clarithromycin resistance (71%). In a recent study exposed that eradication rate is 90-92% for levofloxacin plus rabeprazole and either amoxicillin or tinidazole in a pilot study from Italy (Nicholas *et al.*, 2014; Wong *et al.*, 2006).

In other hands, it is used to fail standard triple and sequential therapy, and levofloxacin therapy is shown that eradication rate is more than 95% for esomeprazole plus amoxicillin followed by esomeprazole plus levofloxacin plus metronidazole for 5 days (Ramesh *et al.*, 2017). It has been postulated that eradication rate 93-96% for esomeprazole, amoxicillin and levofloxacin administration of 7 days (Schrauwen *et al.*, 2009). It is revealed that the cure rate is 90-92% for esomeprazole plus amoxicillin plus a levofloxacin administration for 10 days and their eradication rate is 87%, 91% and 96% study in Germany, Italian, and Netherlands (Skender *et al.*, 2013). Choice of amoxicillin instead of metronidazole because the resistance rate of amoxicillin is minor than metronidazole; but the resistance rate is growing (9-13%) in Korea (Moon *et al.*, 2013).

Levofloxacin, esomeprazole and either amoxicillin or clarithromycin are highly effective and protective against *H. pylori* infection, but the combination with amoxicillin is better tolerated than the combination with clarithromycin. Levofloxacin therapy is fantastic bioavailability, higher eradication rate (more than 90%) and low side effects (Schrauwen *et al.*, 2009). Another same drug group is established that sitafloxacin based therapy is used to eradicate *H. pylori* infection in Japan instead of triple therapy and eradication rate is 70-80% for a PPI, amoxicillin, sitafloxacin (Hirata *et al.*, 2016).

Table 2: Comparisons of the different methods for *H. pylori* infection treatment

Variables	Standard therapy	Sequential therapy	Quadruple therapy	Concomitant therapy	Levofloxacin therapy
Eradication rate	80-90%	63-90%	89.95%	89-93%	90-96%
Antibiotic resistance	More	Low	Lower than standard and sequential	More	Lower than other therapies
Side effects	Low	More than standard therapy	Low	Low	Lower than other therapies
Patients compliance	High	High	High	High	Higher than other therapies

DISCUSSION

A triple therapy is recommended first-line treatment of *H. pylori* infection (Zullo *et al.*, 2010). In Asia and Africa, seven days administration with a PPI, amoxicillin or metronidazole and clarithromycin is the more effective eradication of *H. pylori* infection and their treatment regimens are well-tolerated and improve patient's compliance. At present, triple therapy is efficacy, low caused by antibiotics resistant, especially metronidazole and clarithromycin resistance. But it proved that non-metronidazole regimens are currently regarded and more suitable treatment of *H. pylori* infection in Asia and Africa. It is reported that eradication rate is 90% for clarithromycin, a PPI and amoxicillin for 7-10 days (Wong *et al.*, 2000; Dolapcioglu *et al.*, 2014). In the last decade, 7-10 days triple therapies have unacceptably low cure rates, but higher triple therapy has increased the cure rate as compared to 7-10 day regimen. When first-line therapy failed after a second-line levofloxacin therapy choose which is better efficacy administered for 14 days in the treatment of *H. pylori* infection (De Francesco *et al.*, 2016). At present study, triple therapy failure of *H. pylori* eradication due to antibiotic resistance which resistance rate is more than 20% for clarithromycin, and 40% for metronidazole (Lee *et al.*, 2016). So, alternative treatment is better than first line treatment such as sequential, concomitant Quadruple bismuth and Levofloxacin regimens (De Francesco *et al.*, 2014).

Some studies have shown that sequential therapy is better efficacy for this infection, even there are main facts clarithromycin resistance as a result low eradication rate. Concomitant therapy is major problem dual antibiotic resistance (metronidazole-clarithromycin) after treatment failure, with metronidazole resistance rate is 60% in China-Iran-India, Central and South America (David *et al.*, 2014).

In this regard, levofloxacin therapy is more effective for single or dual antibiotic resistance patients, especially clarithromycin and metronidazole, achieving cure rate is 90% (Federico *et al.*, 2012). It is an appropriate therapeutic approach against *H. pylori* when sequential therapy failed (Zullo *et al.*, 2006). Levofloxacin therapy cure rate is superior to quadruple therapy; it is shown that the eradication rate greater than 90% compared to quadruple therapy with a lower incidence of side effects (Wong *et al.*, 2006; Ierardi *et al.*, 2015).

CONCLUSION

Standard triple, sequential, quadruple bismuth and concomitant are the good therapeutic efficacy of *H. pylori* infection, but recently less effective due to antibiotic resistance and patient compliance. Levofloxacin therapy is a more effective treatment of this infection because low antibiotic rate and eradication rate is higher than other therapy especially metronidazole- clarithromycin resistance.

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